Gerald DeNardo, M.D.
Director, Section of Radiodiagnosis & Therapy
University of California Davis, School of Medicine
Radiodiagnosis & Therapy
1508 Alhambra Blvd., Room 3100
Sacramento, CA 95816

Gerald DeNardo, M.D. is Director, Section of Radiodiagnosis & Therapy at the University of California Davis School of Medicine. He also is a Professor of Radiology at the UCD School of Medicine; Professor of Radiology UCD School of Veterinary Medicine and Professor of Pathology at the UCD School of Medicine. Dr. DeNardo received his M.D. in 1957 from University of California School of Medicine, San Francisco. Dr. DeNardo has authored over 250 articles and is past president of both the American College of Nuclear Physicians and Society of Nuclear medicine.

Use of Copper and Other Novel Isotopes for Lymphoma, Breast and Other Tumor Therapies

Lym-1, a monoclonal antibody that preferentially targets malignant lymphocytes, has induced durable therapeutic remissions in most patients with advanced stage, chemotherapy resistant non-Hodgkin's lymphoma (NHL), regardless of histology, or chronic lymphocytic leukemia (CLL) when labeled with I-131 and used for radioimmunotherapy (RIT). Response rate can be increased by patient selection, and response to ^{131}I-Lym-1 therapy has been associated with increased survival. Therapy proved safe.

Although ^{131}I has played a central role n RIT thus far, some properties of copper-67 (^{67}Cu) are preferable for RIT. ^{67}Cu has beta emissions comparable to those of ^{131}I but gamma emissions more favorable for imaging. The ability to image and treat patients with a single radiopharmaceutical makes ^{67}Cu an attractive option for RIT. The macrocyclic chelating agent, TETA, binds ^{67}Cu selectively and tightly to form a stable radiopharmaceutical *in vivo*. ^{67}Cu-2IT-BAT-Lym-1 exhibited greater uptake and longer retention in tumor resulting in higher radiation dose and better therapeutic indices than ^{131}I-Lym-1. Superior imaging, substantially greater radiation dosimetry to tumor, and a threefold improvement in the therapeutic index was achieved with ^{67}Cu-2IT-BAT-Lym-1 compared to ^{131}I-Lym-1. Remarkably, numerous tumor regressions were observed after imaging doses. The results indicated considerable therapeutic potential for ^{67}Cu-2IT-BAT-Lym-1. Because ^{67}Cu is a novel radionuclide under development, it is not routinely available in quantities sufficient for RIT. In a pilot trial of RIT, ^{67}Cu-2IT-BAT-Lym-1 targeted NHL and provided therapeutic irradiation that resulted in a 58% response rate in patients that had progressive NHL after multiple chemotherapeutic regimens. This trial established ^{67}Cu-2IT-BAT-Lym-1 as safe, effective treatment for patients with NHL. A sustained commitment to ^{67}Cu production and continuing studies of ^{67}Cu for RIT is warranted. Simply stated, multicurie production on a continuous basis is possible on existing accelerators and reactors if there was a mandate.

Like ^{67}Cu, ^{90}Y is an attractive radionuclide for RIT because outpatient treatment is possible and tumor residence time is longer than that for corresponding ^{131}I labeled Mabs. ^{111}In is usually used as a surrogate for ^{90}Y for imaging and dosimetry creating some uncertainty.

References

Rose, L.M., A.H. Gunasekera, S.J. DeNardo, G.L. DeNardo, C.F. Meares. Lymphoma selective antibody Lym-1 recognizes a discontinuous epitope on the light chain of HLA-DR10. Cancer Immunology Immunotherapy 43:26-30, 1996.

DeNardo, G.L., S.J. DeNardo, D.S. Goldstein, L.A. Kroger, K.R. Lamborn, N.B. Levy, J.P. McGahan, Q. Salako, S. Shen, J.P. Lewis. Maximum tolerated dose, toxicity, and efficacy of ^{131}I-

Lym-1 antibody for fractionated radioimmunotherapy of non-Hodgkin's lymphoma. Journal of Clinical Oncology16(10): 3264-3256, 1988.

DeNardo, G.L., S.J. DeNardo, K.R. Lamborn, D.S. Goldstein, N.B. Levy, J.P. Lewis, L.F. O'Grady, A. Raventos, L.A. Kroger, D.J. Macey, J.P. McGahn, S.L. Mills, S. Shen, Low-dose, Fractionated Radioimmunotherapy for B-Cell Malignancies Using ^{131}I-Lym-1 Antibody. Cancer Biotherapy & Radiopharmaceuticals 13: 239-254, 1998.

DeNardo, G.L., R.T. O'Donnell, R.K. Oldham, S.J. DeNardo. A revolution in the treatment of non-Hodgkin's Lymphoma. Cancer Biotherapy & Radiopharmaceuticals 13: 213-223, 1998.

DeNardo, G.L., K.R. Lamborn, D.S. Goldstein, L.A. Kroger, S.J. DeNardo. Increased survival associated with radiolabeled Lym-1 therapy for non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Cancer 80 Suppl 2706-12, 1997.

DeNardo, G.L., S.J. Denardo, D.L. Kukis, R.T. O'Donnell, S. Shen, D.S. Goldstein, L.A. Kroger, Q Salako, D.A. DeNardo, G.R. Mirick, L.F. Mausner, S.C. Srivastava, C.F. Meares. Maximum tolerated dose of ^{67}Cu-2IT-BAT-Lym-1 for fractionated radioimmunotherapy of non-Hodgkin's lymphoma: a pilot study. Anticancer Research 18:2779-2788, 1998.

DeNardo, S.J., DeNardo, D.L. Kukis, S. Shen, L.A. Kroger, D.A. DeNardo, D.S. Goldstein, G.R. Mirick, Q. Salako, L.F. Mausner, S.C. Srivastava, C.F. Meares. ^{67}Cu-2IT-BAT-Lym-1 pharmacokinetics, radiation dosimetry, toxicity and tumor regression in patients with lymphoma. Journal of Nuclear Medicine, 1998.

Richman, C.M., S.J. DeNardo, L.F. O'Grady, G.L. DeNardo. Radioimmunotherapy for breast cancer using escalating fractionated doses of iodine-131 chimeric L6 antibody with peripheral blood progenitor cell transfusions. Cancer Research 55 Suppl:5916-5920, 1995.

DeNardo, S.J., L.F. O'Grady, C.M. Richman, D.S. Goldstein, R.T. O'Donnell, D.A. DeNardo, L.A. Kroger, K.R. Lamborn, K.E. Hellstrom, I. Hellstrom, G.L. DeNardo. Radioimmunotherapy for advanced breast cancer using I-131-ChL6 antibody. Anticancer Research 17:1745-1752, 1997.

DeNardo, G.L., L.A. Kroger, C.F. Meares, C.M. Richman, Q. Salako, S. Shen, K.R. Lamborn, J.J. Petersen, L.A. Miers, G.R. Zhong, S.J. DeNardo. Comparison of DOTA-peptide-ChL6, a novel immunoconjugate with catabolizable linker, to 2IT-BAD-ChL6 in breast cancer xenografts. Clinical Cancer Research 4:2483-2490, 1998.

DeNardo, S.J., C.M. Richman, D.S. Goldstein, S. Shen, Q. Salako, D.L. Kukis, C.F. Meares, A. Yuan, J. Welborn, G.L. DeNardo. Yittrium-90/Indium-111-DOTA-peptide-chimeric L6: pharmacokinetics, dosimetry and initial results in patients with incurable breast cancer. Anticancer Research 17:1735-1744, 1997.

DeNardo, S.J., E.L. Kramer, R.T. O'Donnell, C. Richman, Q.A. Salako, S. Shen, M.E. Noz, S.D. Glenn, R.L. Ceriani, G.L. DeNardo. Radioimmunotherapy for breast cancer using Indium-111/Yittrium-90 BrE-3: results of a phase one clinical trial. Journal of Nuclear Medicine 38:1180-1185, 1997.